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Out of balance: how a binaural coincidence detection circuit responds to unilateral deafferentation

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Coincidence detection is a fundamental computation used by neurons to determine when two or more sources of input are active within a brief time window. Optimal coincidence detection generally requires a delicate balance of synaptic strengths, so that no single source of input dominates the computation. But what happens when one source of input is weakened by injury to an afferent pathway? Does homeostatic plasticity drive synaptic scaling to restore balance, or do alternative mechanisms further suppress the damaged pathway, which may no longer carry reliable information? In this issue of *The Journal of Physiology*, Lu and colleagues address these important questions by examining how binaural coincidence detector neurons in the chick nucleus laminaris (NL) respond to unilateral cochlear ablation (Lu *et al.* 2018). Their results reveal a surprising case of anti-homeostatic plasticity in which synapses from the deafferented pathway, despite being significantly weaker than those from the control pathway, are more strongly suppressed by metabotropic glutamate receptor (mGluR)-mediated inhibition of synaptic release.

NL neurons, like their analogues in the mammalian medial superior olive (MSO), use coincidence detection to compare the arrival times of sounds between the two ears. This comparison underlies detection of interaural time differences (ITDs), which are important cues for horizontal sound localization. Due to the speed of sound and head geometry, ITDs typically vary over a submillisecond range ($\pm 700\ \mu s$ for humans and $< \pm 100\ \mu s$ for chicks). This means that NL and MSO neurons must be exquisitely sensitive coincidence detectors, and indeed, both modulate their firing rate as ITDs vary over tens to a few hundreds of microseconds. Among many specializations that make this possible, two are particularly relevant here. First, NL and MSO neurons are bipolar neurons: one dendrite receives excitatory synaptic input from the ipsilateral cochlear nucleus and the other from the contralateral cochlear nucleus. This separation of inputs enhances coincidence detection because each dendrite acts as a current sink for the other dendrite (Agmon-Snir *et al.* 1998). Second, under normal hearing conditions, excitatory synaptic inputs from the left and right cochlear nuclei exhibit similar strength and kinetics (Funabiki *et al.* 1998; Franken *et al.* 2015). This synaptic balance enhances coincidence detection by limiting saturation of voltage changes within individual dendrites (Dasika *et al.* 2007).

Lu and colleagues confirmed and extended these results, showing that bilateral inputs to NL neurons are balanced in numerous ways. In acutely prepared chick brain slices, the investigators made whole cell recordings from NL neurons while separately stimulating inputs from the ipsilateral and contralateral cochlear nuclei magnocellularis (NM). They found that bilateral excitatory postsynaptic currents (EPSCs) were well matched in their amplitudes and kinetics and exhibited similar patterns of short term depression. A previous study showed that activation of group II mGluRs inhibited synaptic release onto NL neurons (Okuda *et al.* 2013). Lu and colleagues built on these results, finding that EPSC amplitudes were inhibited by both group I and group II mGluR agonists. This inhibition was also well matched between the ipsilateral and contralateral pathways.

Modelling studies have predicted that the balanced properties of synaptic inputs to NL and MSO neurons should promote linear integration of bilateral synaptic events (Agmon-Snir *et al.* 1998; Dasika *et al.* 2007). To test this prediction, Lu and colleagues took advantage of a favourite trick of synaptic physiologists: using short term plasticity to show that individual sources of input could be independently activated. This allowed the investigators to directly test whether combined activation of ipsilateral and contralateral NM projections yielded linear integration of synaptic events. In current clamp recordings, the authors confirmed the model predictions, finding that bilateral integration of excitatory postsynaptic potentials (EPSPs) was approximately linear.

What happens to this balance when one input pathway is deafferented? Lu and colleagues tested this by removing the cochlea from one side of the head, then examining synaptic responses in NL neurons 1–3 days later. Unilateral deafferentation caused a dramatic reduction in the amplitudes of EPSCs evoked from the damaged pathway. Despite this reduction, synapses from the damaged pathway continued to exhibit short term depression comparable to that from the control pathway. Surprisingly, in the region of NL that responds to low frequency sounds, activation of group II mGluRs more strongly inhibited synapses from the damaged pathway than from the control pathway. This increased inhibition was accompanied by a selective increase in group II mGluR expression in the neuropil where synapses from the damaged pathway reside.

Together, these results reveal a fascinating case of anti-homeostatic plasticity. Under control conditions, synaptic properties were carefully balanced to promote the linear integration required for binaural coincidence detection. Following unilateral cochlear ablation, this balancing act went off kilter. Synapses from the deafferented pathway were both weakened and more strongly inhibited by activation of group II mGluRs. Going forward, it will be important to address the mechanisms underlying these changes and how long they persist. A critical question is why do these mechanisms exist in the first place? An intriguing possibility is that in certain systems, anti-homeostatic mechanisms decrease the influence of inputs that no longer carry meaningful information. If this is the case, it will be important to understand how such mechanisms respond to interventions, such as cochlear implants, that aim to restore afferent drive.

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Additional information

Competing interests

None declared.